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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/831,534	06/18/2001	Bryan John Smith	1300-1-008	5753

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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 11/05/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/831,534	SMITH, BRYAN JOHN	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2002 and 16 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8*. Filed 9/16/03
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's amendment filed 6/18/02 and 6/16/03 are acknowledged and have been entered.

Claims 14-20 are pending.

2. Applicant's election of a hybrid protein having the antigen-antibody fragment linked to an albumin molecule or fragment thereof, the linkage being by a bridging molecule between the thiol groups of a cysteine residue that is present in the antibody and another such residue present in albumin at position 34, in the amendment filed 6/16/03 is acknowledged.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 14-20 read upon the elected species and are currently being examined.

3. The disclosure is objected to because of the following informalities:

The use of the trademarks GAMMABIND AND SEPHADEX have been noted in this application on pages 21 and 22, respectively. They should be capitalized or accompanied by the ™ or ® symbol wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Each letter of the trademark must be capitalized. See MPEP 608.1(V) and Appendix 1.

Appropriate corrections are required.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 14-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the applicant had possession at the time of invention of the claimed hybrid protein/composition thereof, comprising one antigen binding antibody fragment covalently linked to a fragment of albumin, including at position 34 of albumin.

The specification discloses (on page 3 at lines 20-31) that the hybrid proteins of the invention have the antigen binding capabilities of an antibody fragment and the longevity of serum albumin in vivo. The specification does not disclose any working examples of fragments of albumin coupled to antibody fragments.

The instant claims encompass conjugates comprising a fragment of an albumin molecule, and potentially one which does not include position 34. There is insufficient disclosure in the specification on conjugates comprising such albumin fragments.

In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. However, a generic statement such as " fragment" is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by the property of being some portion of albumin. It does not specifically define any of the compounds that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others, nor which portions are required for function, i.e., increasing the half-life of the antibody fragment. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus.

One of ordinary skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

6. Claims 14-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected to make and/or use the invention.

The specification does not disclose how make and or/use a hybrid protein/composition thereof, comprising one antigen binding antibody fragment covalently linked to a fragment of albumin, including at position 34 of albumin. The specification has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass hybrids of undisclosed structure that may not provide the desired function of longevity of serum albumin in vivo.

The specification discloses (on page 3 at lines 20-31) that the hybrid proteins of the invention have the antigen binding capabilities of an antibody fragment and the longevity of serum albumin in vivo. The specification does not disclose any working examples of fragments of albumin coupled to antibody fragments.

The instant claims encompass conjugates comprising a fragment of an albumin molecule, and potentially one that does not include position 34. There is insufficient disclosure in the specification on conjugates comprising such albumin fragments.

Evidentiary reference Peters (IDS reference "AT") discloses a 27 day half life of serum albumin in vivo in humans.

There is insufficient guidance in the specification as to how to make and/or use the instant invention. There is no disclosure in the specification as to which fragments of albumin would result in functional hybrid proteins. Undue exprimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 14-20 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 14 is indefinite because there is no recitation of "or fragment thereof" after the second occurrence of albumin in line 2.

b. Claim 15 is indefinite in the recitation of "around 10A to around 20A in length" because it is not clear what the metes and bounds of "A" are. It is suggested that Applicant amend said claim to recite the symbol for angstroms disclosed in the instant specification on page 12 at lines 13-14.

9. For the purpose of prior art rejections, the filing date of the instant claims 15 and 17-20 are deemed to be the filing date of the PCT application PCT/GB99/03747, i.e., 11/10/99, as the 9824632.5 application does not support the claimed limitations of the instant application. The limitation "wherein the bridging molecule is from around 10A to around 20A in length" is not disclosed in the 9824632.5 application.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 14-20 are rejected under 35 U.S.C. § 103(a) as obvious US Patent No. 6,350,431 in view of Peters (IDS reference "AT") and the known facts disclosed in the specification on page 27 at lines 9-13.

US Patent No. 6,350,431 discloses a polymeric targeting radioactive immunoreagent/pharmaceutical compositions thereof, comprising a metal radionuclide ion (i.e., an effector group as disclosed on page 9 of the instant specification at lines 5-14), a linking group and an immunoreactive group (i.e., vector) which is attatched through a linking group to the polymer (especially column 21 at lines 45-50). US Patent No. 6,350,431 further discloses that the immunoreagent can be an antibody, or a fragment thereof such as Fab or Fab'2 (especially column 25 at lines 6-11, column 23 at lines 4-8 and lines 44-54), that the linking group may be optionally substituted hexylene (especially column 43 at line 27-67, column 44 at lines 1-19 and column 45 at lines 49-60) and that the linking group may comprise albumin (especially column 48 at lines 12-13). US Patent No. 6,350,431 discloses that the vector reactive group can be selected from a sulfhydryl group such as a cysteine sulfhydryl group commonly found on a protein or other biological molecule (especially paragraph spanning columns 27 and 28).

US Patent No. 6,350,431 does not disclose that the indirect linking is between the thiol groups of a cysteine residue present in the antibody and another present in the albumin at position 34.

Peters teaches the presence of a free cysteine in albumin (especially paragraph spanning pages 164 and 165).

The known facts disclosed in the specification on page 27 at lines 9-13 are that serum albumin has one cysteinyl residue that is not engaged in a disulphide bond, i.e., at position 34 in mature human albumin.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made with regard to the immunoreagent disclosed by US Patent No. 6,350,431 to have attached the linking (bridging) molecule at position 34 in the albumin since the cysteine is free and the remainder of the cysteines are involved in intrachain disulfide bonds as taught by Peters.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to produce a pharmaceutical immunoreagent such as the one disclosed by US Patent No. 6,350,431 wherein the native structure of the albumin carrier was retained by non-disruption of intrachain disulfide bonds as taught by Peters. Claim 15 is included in this rejection because the linking molecules disclosed by US Patent No. 6,350,431 range from "around 10A[angstroms] to around 20 A[angstroms] in length" recited by the instant claim. Claim 17 is included in this rejection because it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have extended the Fab at the CH1 carboxy terminus to include the cysteine involved in the interchain disulfide bond of the intact antibody in order to utilize the cysteine in disulfide binding without disrupting intrachain disulfide bonds.

12. Claims 14, 15 and 17-20 are rejected under 35 U.S.C. § 103(a) as obvious US Patent No. 4,751,286 in view of US Patent No. 4,749,570, Peters (IDS reference "AT") and the known facts disclosed in the specification on page 27 at lines 9-13.

US Patent No. 4,751,286 discloses use of a bridging molecule to attach the reduced disulfide bonds of a monoclonal antibody or fab to a toxin or a drug, and the mAb-bridging molecule-toxin conjugate (especially column 8 at lines 21-26), and the bridging molecule itself may bear a label (especially column 3 at lines 5-8). US Patent No. 4,751,286 discloses the use of the bridging molecule is designed to preserve the native protein structure (especially column 2 at lines 58-61).

US Patent No. 4,751,286 does not disclose an antibody conjugated to albumin wherein the antibody and albumin are indirectly linked by the bridging molecule between the thiol groups of a cysteine residue present in the antibody and another present in the albumin at position 34.

US Patent No. 4,749,570 discloses the conjugation of albumin to therapeutic agents such as antibodies to increase their resistance to bioinactivation (especially column 2).

Peters teaches the presence of a free cysteine in albumin (especially paragraph spanning pages 164 and 165).

The known facts disclosed in the specification on page 27 at lines 9-13 are that serum albumin has one cysteinyl residue that is not engaged in a disulphide bond, i.e., at position 34 in mature human albumin.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have conjugated albumin disclosed by US Patent No. 4,749,570 to the antibody conjugate disclosed by US Patent No. 4,751,286 by the cysteine of the monoclonal antibody as taught by US Patent No. 4,751,286 and the cysteine at position 34 in albumin taught by Peters and the said admissions in the specification.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to produce an antibody conjugate as disclosed by US Patent No. 4,751,286 which is more resistant to bioinactivation by coupling to albumin as disclosed by US Patent No. 4,749,570 that retains the native structure of the albumin carrier by non-disruption of intrachain disulfide bonds as taught by Peters and the said admissions in the specification. Claim 15 is included in this rejection because the linking molecules disclosed by US Patent No. 6,350,431 range from "around 10A[angstroms] to around 20 A[angstroms] in length" recited by the instant claim. Claim 17 is included in this rejection because it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have extended the Fab at the CH1 carboxy terminus to include the cysteine involved in the interchain disulfide bond of the intact antibody in order to utilize the cysteine in disulfide binding without disrupting intrachain disulfide bonds.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 703-308-0061. The Examiner can normally be reached on Monday and Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Chan, can be reached on (703) 308-3973. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306 (before final) or 703-872-9307 (after final).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

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October 24, 2003

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